

CARCINOMA OF THE BREAST

II—CRITERIA OF OPERABILITY (CONTINUED)

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EDEMA OF THE SKIN

EDEMA OF THE SKIN over the breast is an exceedingly important sign of the extent of breast carcinoma, the significance of which is not generally recognized by surgeons.

It was first described by French surgeons almost a century ago. Lannelongue⁵ gives the great surgeon and surgical pathologist, Auguste Nélaton, the credit for originating the apt descriptive term "*peau d'orange*" that has kept its place in medical nomenclature through the years. Figure 1 illustrates this striking appearance.

Sir William Banks,^{6, 7} a distinguished Liverpool surgeon, who was one of the pioneers during the last quarter of the 19th century in emphasizing the necessity for radical surgical attack upon breast carcinoma, compared the appearance of such edematous skin to saddle leather, and called it "pig-skin." He offered the explanation that the fine points in its surface are "the hair follicles caught and tucked down by the cancer." His contemporary, Thomas Bryant,⁸ of Guy's Hospital, who, in 1887, published a little book on diseases of the breast, which was the best thing of its kind that had been done up to that time, preferred the term *edema* of the skin. He pointed out that such edema is one of the features of a particularly malignant form of breast carcinoma which he called "acute edematous infiltration of the skin and breast" or "brawny infiltration." His description of this form of the disease, which today has come to be called the *inflammatory type* was an excellent one, and was illustrated with a colored drawing.

Although Bryant was a skilled clinician he was not much of a microscopist. Indeed, his understanding of the pathologic processes involved in the spread of breast cancer was rudimentary. He did not understand the mechanism of metastasis by tumor emboli, and conjectured that carcinoma spread by what he called "infection," that is "the acquired power possessed by morbid epithelial cells, when coming into contact with embryo undeveloped cells, of influencing their development, and causing them to take on the epithelial form."

Bryant was writing in terms of gross pathology when he wrote regarding the acute "brawny infiltration" form of breast carcinoma: "These local symptoms are always associated with rapidly progressing disease, in which the original nidus not only spreads rapidly by infiltration, or 'local infection' but also by 'lymphatic infection,' the lymphatics, as described, being apparently filled, if not choked, with the epithelial material which it is conveying

to the lymphatic glands.” This observation of Bryant’s was certainly an astute one, even though it was not based upon microscopic studies, and should not be interpreted as an explanation of the microscopic changes responsible for skin edema.

The first to study the phenomenon of skin edema from the microscopic point of view was Archibald Leitch.⁹ During the years he spent at Middlesex he became interested in the problem of acute mammary cancer and he made



FIG. 1.—Close-up view of edema of the skin over the breast.

sections of the skin in several cases in which there was extensive edema of it. He saw that the corium was enormously thickened by edema. The arterioles were dilated, and many were filled with cancer cells. There was a marked perilymphatic infiltration of lymphocytes and plasma cells. Leitch described these findings in a paper published in 1909 entitled “*Peau D’Orange* in Acute Mammary Carcinoma: Its Cause and Diagnostic Value.” He concluded that the cancer cells had permeated the skin lymphatics in the opposite direction of the lymph stream, blocking the lymphatic circulation of the skin and causing edema of it. The depressions in the edematous skin were the exaggerated pits of the hair follicles.

Recent writers on inflammatory carcinoma of the breast, such as Taylor and Meltzer,¹⁰ have accepted Leitch’s interpretation that its essential feature

is a subepidermal carcinomatous lymphatic permeation. The disease has come to be fairly well known to surgeons as an extraordinarily malignant form of breast cancer, which is recognizable by the generalized enlargement of the breast and the extensive redness and edema of the skin over it.

No one, however, has given special attention to the phenomenon of edema of the skin in itself, and to its prognostic significance. It is not generally appreciated that this important clinical sign is seen in the later stages of all forms of breast carcinoma, whether they be rapid or slow in growth rate. These are the features which we wish to emphasize.

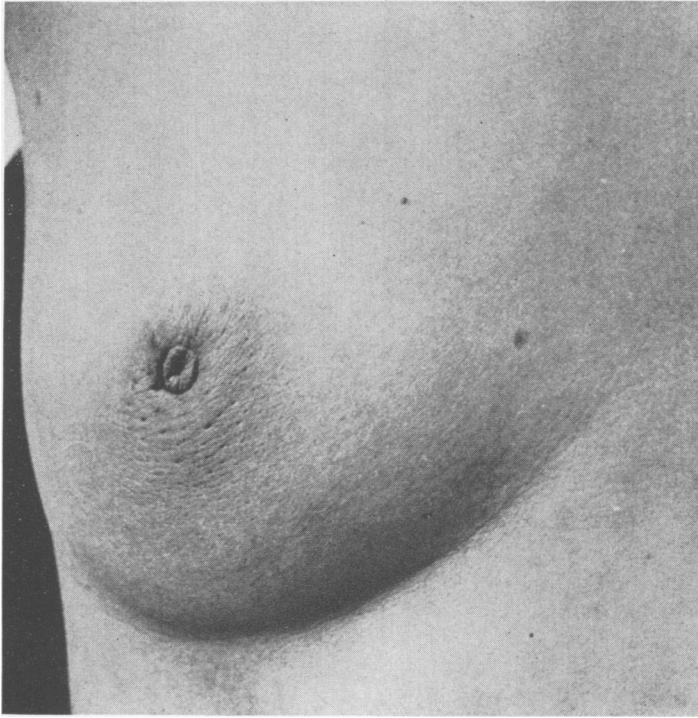


FIG. 2.—A small area of edema of the skin in the areolar region.

When the area of edema is small, as in the case shown in Figure 2, it easily escapes detection unless carefully looked for. It usually begins in the skin within or just caudad to the areola, that is, in the more dependent part of the breast. This is regularly the site where edema first appears when the tumor is situated deep in the central part of the breast, but it may also be the earliest location of edema when the tumor is situated in the periphery of the breast. We have seen edema appear just below and medial to the areola when the carcinoma was a small one situated in the extreme upper outer limits of the breast.

This tendency for edema of the skin to develop in the areolar region is very likely due to the fact that the carcinoma of the breast tends to spread, in its late stages, in a retrograde direction along the main lymphatic pathways

accompanying the ducts converging at the nipple. Reaching the dermal lymphatics in the areolar region the carcinoma plugs them so completely that edema in the immediately adjacent dependent area of skin results.

There are, of course, other cases in which the edema first appears in the skin immediately over a carcinoma situated more peripherally in the breast. In such cases the skin is usually somewhat adherent to the underlying tumor, and it seems probable that the skin lymphatics have been obstructed by direct retrograde invasion from the surface of the growth outwards.

We have been much interested in the mechanism by which edema of the skin is produced, and we have made a special effort over a period of years

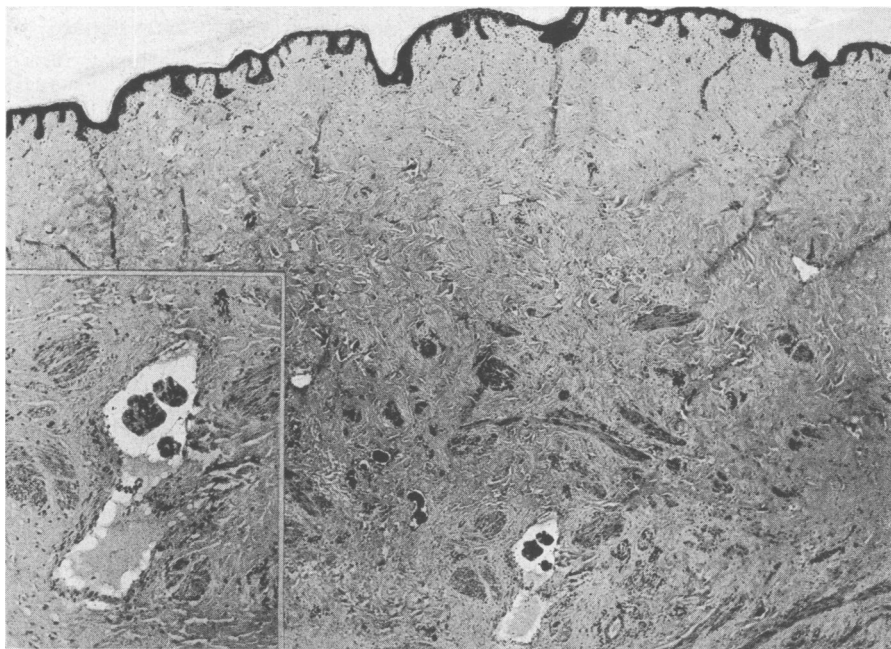


FIG. 3.—Carcinoma emboli in dilated lymphatics in the corium of edematous skin.

to study the skin histologically in these cases. In interpreting the findings the first requisite, of course, is an appreciation of the normal arrangement of the lymphatics in the skin. Since the classical studies of von Teichmann,¹¹ it has been known that there are no lymphatics in the epidermis itself. In the corium, however, there are two networks of them, a narrow-meshed superficial one which sends branches up around the papillae, and a wide-meshed deeper one made up of broader channels equipped with valves which communicate by means of vertical branches with the subdermal lymphatics. Our histologic studies of edematous skin have led us to the conclusion that the process begins with the appearance of embolic masses of carcinoma cells in the deep network of lymphatics in the corium. We assume that the mechanism by which extension takes place is at first *embolic* rather than one of *continuous permeation*, because we have often seen the picture illustrated in

Figure 3. Here, in edematous skin, the deeper lymphatics are dilated and contain unmistakable tumor emboli. As the edema progresses both the superficial and deep lymphatic vessels become solidly choked with tumor cells, and at this advanced stage of the process permeation is probably the predominant mechanism by which the disease extends.

Leitch, and all those who have written regarding inflammatory carcinoma since his time, have assumed that edema is due to continuous permeation of the skin lymphatics by the carcinoma. Leitch records studying a total of only seven cases in which there was edema, and all of these were apparently far advanced, so that he may not have had the opportunity of studying the histologic appearance of the early stage of edema. It is probable, also, that Leitch was influenced toward emphasis upon permeation as opposed to embolism as the method by which breast carcinoma spreads by his confrere Sampson Handley. For, in 1905, when Leitch was studying cases with edema, Sampson Handley was working in the same laboratory at Middlesex, completing his interesting investigations of the process of dissemination of breast carcinoma.

When edema involves a large area of skin over the breast, the dermal and subdermal lymphatics are extensively involved. This explains the clinical fact that patients with edema involving a considerable part of the skin over the breast are never cured by surgery. When tumor embolism and permeation have progressed to such an advanced stage it is only reasonable to find that the disease is beyond the limits of any local surgical attack, no matter how radical it may be. This, at least, has been our experience at the Presbyterian Hospital.

In order to determine as accurately as possible the significance of edema of the skin we classified the cases in which this phenomenon was present into two groups: (1) Those in which the extent of the edema was *limited to less than one-third of the skin over the breast*; and (2) those in which it *extended over a larger area*.

There were a total of 41 patients with *extensive* edema of the skin in whom radical mastectomy was performed. Twenty-seven, or 65.9 per cent, were known to have developed local recurrence within five years following operation. None remained cured at the end of five years. We have, therefore, placed this group of cases in our *categorically inoperable* class.

The results of radical mastectomy in the patients with *limited* edema are shown in Table XIV, from which the groups of cases classified by us as *categorically inoperable* have been excluded.

TABLE XIV
RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THERE WAS LIMITED EDEMA OF THE SKIN OVER THE BREAST
(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Limited edema <i>only</i>	32	13	40.6%	4	12.5%
Limited edema, <i>with</i> other signs of locally advanced disease.....	17	12	70.6%	0	
Total.....	49	25	51.0%	4	8.2%

These data indicate that edema of the skin, even when it is of very limited extent, is an extremely serious sign. In the group of cases in which this grave sign occurred alone the cure rate was but 12.5 per cent, and when it occurred in conjunction with other signs of locally advanced disease there were no cures.

When we state that edema is a grave sign we mean, of course, that it is a grave sign when it is produced by carcinoma. For edema of the skin over the breast develops, although infrequently, in a variety of other conditions. It is sometimes seen, for instance, when the axillary lymph nodes are extensively involved by tuberculosis. Breast abscess produces it. We have also seen it develop in association with a cyst around which there was a marked granulomatous proliferation. In these conditions the lymphatic blockage must be due to the inflammatory process. The diagnostician should take care not to jump to the conclusion that a patient has carcinoma just because she has edema, for in itself this sign is not diagnostic.

FIXATION OF THE TUMOR TO THE CHEST WALL

As carcinoma of the breast extends locally, the growth itself, as well as the breast in which it lies, tends to become fixed to the underlying pectoral fascia, and finally to the thoracic cage. It is important to define this fixation in terms of degree. All surgeons are familiar with the advanced degree of fixation in which the breast is more or less immovable upon the chest wall. But the early stage of the process often escapes the examiner's attention, for it is brought out only by certain special maneuvers.

Early fixation can be demonstrated by having the patient sit erect, place her hands on her hips, and contract her pectoral muscles by pressing her hands against her sides first on one side and then on the other. The breasts, if they are not too heavy, are normally pulled upward slightly by this action. The upward motion is usually apparent only along the lateral aspect of the breast where the movement of the underlying pectoral muscle is greatest. There is usually no upward movement of the lower, dependent edge of the breast. But when carcinoma has produced abnormal fixation of the breast to the underlying pectorals the affected breast is pulled upwards more than its normal mate. This abnormal elevation may be apparent only along the lateral aspect of the breast, or in the region of the tumor. In cases with more advanced fixation the whole breast may be elevated by pectoral contraction. This is what we have chosen to designate as first-degree fixation. The breast and the tumor within it can still be moved passively with freedom over the chest wall.

Another maneuver to demonstrate abnormal fixation of the tumor to the chest wall is carried out with the patient lying supine, the hands placed on the hips. With the pectorals relaxed, the examiner first tests the movability of the tumor over the chest wall by gently moving it upwards and downwards in the direction of the long axis of the body. The patient is then asked to press her hands against her sides, contracting the pectorals,

and the movability of the tumor over the chest wall is again tested. When this maneuver shows that movability is decreased by contraction of the pectorals we assume that it is due to abnormal fixation to the underlying pectoral fascia, and designate it in our classification as second-degree fixation.

A more advanced degree of fixation, and one which we call third-degree fixation, is that in which the tumor is more or less solidly fixed to the underlying chest wall, even when the pectorals are relaxed.

In general, the surgeons who described the physical findings, in years gone by, in the series of cases we are here discussing did not distinguish the lesser degrees of fixation which we have mentioned. We have had to be content, therefore, with sorting out only the group of cases in which the tumor was solidly fixed to the chest wall. The results of treatment in this group, excluding the *categorically inoperable* cases, are shown in Table XV. These results indicate that a marked degree of fixation is a grave sign.

TABLE XV

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THE TUMOR WAS SOLIDLY FIXED TO THE CHEST WALL

(Categorically Inoperable Cases Excluded)

Clinical Group	No. of Cases	5-Year Local Recurrence No.	5-Year Local Recurrence Per Cent	5-Year Clinical Cures No.	5-Year Clinical Cures Per Cent
Fixation <i>only</i>	18	7	38.9%	2	11.1%
Fixation, <i>with</i> other signs of locally advanced disease.....	24	9	37.5%	2	8.3%
Total.....	42	16	38.1%	4	9.5%

There is a small group of cases of carcinoma developing in the inframammary fold which we have not included in Table XV, because they present a special problem as regards fixation. These tumors of the inframammary fold all appear to be fixed, even when they are small, because of the close attachment of the fascial planes to the body wall at this point. The breast, being an appendage of the skin, is enclosed between the superficial and deep layers of the superficial fascia. These layers fuse at the lower border of the breast and bind its edge to the fascial plane of the abdominal wall. In the present series there were five patients with fixed inframammary tumors in whom radical mastectomy was performed. One of them developed a local recurrence, but the other four, or 80 per cent of the group, were cured five years after operation. With this experience in mind, we do not attach any importance to fixation if the tumor is a small inframammary one.

SATELLITE TUMOR NODULES IN THE SKIN OVER THE BREAST

In the advanced stage of mammary carcinoma satellite tumor nodules frequently develop in the skin adjacent to the primary tumor. They are often better felt than seen, being detected by passing the flat of the hand gently over the skin surface. These nodules no doubt develop as the result of retrograde extension of the disease to the skin lymphatics.

The grave significance of the appearance of these satellite skin nodules

is known to most surgeons. In the present series of cases such nodules were noted in a total of 35 of the patients on their admission. Radical mastectomy was performed in only seven. Four of these developed local recurrence, and none was cured. This experience would indicate, therefore, that the presence of satellite nodules is a definite contraindication to radical mastectomy. We include this group of cases in our *categorically inoperable* class.

INTERCOSTAL OR PARASTERNAL NODULES

Secondary nodules of breast carcinoma sometimes appear along the intercostal spaces or in the parasternal region. Their origin must be from the external or the internal intercostal lymphatics, which course posteriorly and anteriorly, respectively, beneath the intercostal muscles. The nodules appear, presumably, when masses of tumor cells become lodged at some particular point along these comparatively large lymphatic channels, and grow to form a secondary tumor nodule that becomes apparent externally. At the sternal edge such nodules lie at the point where the lymphatic channels perforate the chest wall to reach the internal mammary chain of nodes.

It has been our experience that cases in which such secondary intercostal or parasternal nodules are present are beyond the scope of surgery. In the present series of cases radical operation was undertaken in only one such case, and cure was not obtained. We have, therefore, put these cases in our *categorically inoperable* class.

MASSIVELY ENLARGED AXILLARY NODES

Although the accuracy with which the size and consistency of axillary lymph nodes can be determined clinically depends to a considerable extent upon the obesity of the patient, we believe that a careful estimation of their actual size in terms of centimeters should always be attempted. Measurement of the *vertical* diameter of a mass of axillary nodes does not mean a great deal, for a chain of small- or medium-sized nodes fused together may extend a relatively long distance vertically. The estimation of the *transverse* diameter of the largest node or mass of nodes is more truly indicative of the extent of disease, and it is upon this measurement that our experience has taught us to rely.

In the series of cases which we are considering here the examiner usually failed to record actual clinical measurements of the nodes, being content to state that they were moderately or massively enlarged. Unfortunately, statements of this kind do not lend themselves to statistical analysis because massive enlargement means one thing to one examiner and something else to another. There were only 24 cases in our series treated by radical mastectomy in which the transverse diameter of the largest axillary node was recorded as being 2.5 cm., or more. These data, even though they are not large, are worthy of close attention.

In all but one of these patients histologic examination after operation confirmed the presence of metastases. This one patient presented certain unusual features. She was a woman, age 30, with a large, relatively circumscribed tumor occupying the upper central part of the breast. The tumor measured 8 x 10 cm. but it was freely movable over the underlying chest wall and there was no edema of the overlying skin. Massively enlarged but movable lymph nodes were visible in the axillary, and in infraclavicular and supraclavicular regions on the tumor side. These nodes measured as much as 3 cm. in diameter. When radical mastectomy was performed the surgeon was surprised to find that none of these greatly enlarged nodes contained metastases, and the woman remains well, ten years after operation. In retrospect, it can be said that the only clinical feature of this case that justifies classifying it as inoperable was the massive lymph node enlargement. If biopsy of the most prominent nodes had been done it would have shown them to be free of metastases, and the radical mastectomy would then have been in order. This experience leads us to recommend biopsy whenever massive enlargement of axillary nodes is the deciding factor in judging operability.

In the remaining 23 cases in the present series in which clinical measurement of the axillary nodes showed them to be 2.5 cm., or more, in transverse diameter radical mastectomy gave very poor results, particularly in the group of cases in which the factor of large nodes was combined with other signs of locally advanced disease. These data are shown in Table XVI, which does not include the cases classified by us as *categorically inoperable*.

TABLE XVI

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THE AXILLARY LYMPH NODES MEASURED 2.5 CM., OR MORE, IN TRANSVERSE DIAMETER CLINICALLY AND CONTAINED METASTASES

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
2.5 cm. lymph nodes <i>only</i>	10	2	20.0%	2	20.0%
2.5 cm. lymph nodes, <i>with</i> other signs of locally advanced disease.....	13	8	61.5%	1	7.7%
Total.....	23	10	43.5%	3	13.0%

FIXATION OF AXILLARY LYMPH NODES

As involvement of the axillary lymph nodes by carcinoma progresses the disease breaks through the capsule of the nodes and invades the fat and connective tissue of the axilla. Finally, a stage is reached in which the involved nodes become fused together and fixed to the overlying skin and immobile upon the chest wall forming the inner wall of the axillary space. This condition is easy for the examiner to detect in thin patients, but presents more difficulty in obese ones. The fixation to the axillary skin may be apparent as a zone of skin dimpling, and thus forms a visible sign.

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TABLE XVII

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH AXILLARY NODES WERE FIXED TO SKIN OR CHEST WALL

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local No.	Recurrence Per Cent	5-Year No.	Clinical Cures Per Cent
Fixed axillary nodes <i>only</i>	7	1	14.3%	1	14.3%
Fixed axillary nodes, <i>with</i> other signs of locally advanced disease.....	14	7	50.0%	0	
Total.....	21	8	38.1%	1	4.8%

The significance of fixation of the nodes to the skin or the chest wall in cases in the present series treated by radical mastectomy is shown in Table XVII. The groups of cases classified by us as *categorically inoperable* have been omitted from this table. It will be seen that the results of operation in these cases with fixed axillary nodes were very poor. There were no cures at all in the group of cases in which this feature of fixed axillary nodes occurred in combination with other signs of locally advanced carcinoma.

EDEMA OF THE ARM

Edema of the arm is a sign that develops only when the axillary metastases of breast carcinoma have progressed to the stage in which they effectively block the lymphatic pathway through the axilla. The arm then begins to swell and often becomes painful. We have never known of a case in which this sign was present to be cured by radical mastectomy. In the present series operation was performed in three such cases, and none was cured.

This experience has led us to place patients who present themselves with edema of the arm in our *categorically inoperable* group.

It might be added that the edema of the arm that develops *following radical mastectomy* is a very different process. There is often an inflammatory element in the causation of this kind of edema. It ordinarily has no special prognostic significance.

SUPRACLAVICULAR METASTASES

At the turn of the century, Halsted,¹² who devised the first truly radical mastectomy, had extended his operation to include dissection of the supraclavicular region. He omitted it only in the hopeless cases, in "duct cancers," and in the well-differentiated adenomatous types of tumor in which the axilla was not involved. By 1907, when he reported the three-year end-results in his series of 232 cases, he had performed supraclavicular dissection in 119 cases. In 44 of these 119 cases the supraclavicular nodes, as well as the axillary nodes, were proved to be involved. Three of these 44 patients were well three years after operation.

Despite Halsted's endorsement of supraclavicular dissection, the operation has lost favor, and is today generally abandoned, even by most of Doctor Halsted's pupils. Whether this is because present-day surgeons are unwilling to perform an operation that yielded only a seven per cent cure rate even

in Doctor Halsted's hands, or whether their results with the operation have not been as fortunate as his, is difficult to say. It seems more likely that the latter is the best explanation. Eggers¹³ has recently reported his results with supraclavicular dissection in breast carcinoma. He performed the operation upon 14 patients in whom supraclavicular nodes were palpable. None of them survived beyond four years.

In our data from the Presbyterian Hospital the results of supraclavicular dissection in cases with clinically involved supraclavicular nodes were equally discouraging. In a total of 48 of the 986 patients for whom detailed records were available, enlarged supraclavicular nodes were discovered on admission ;

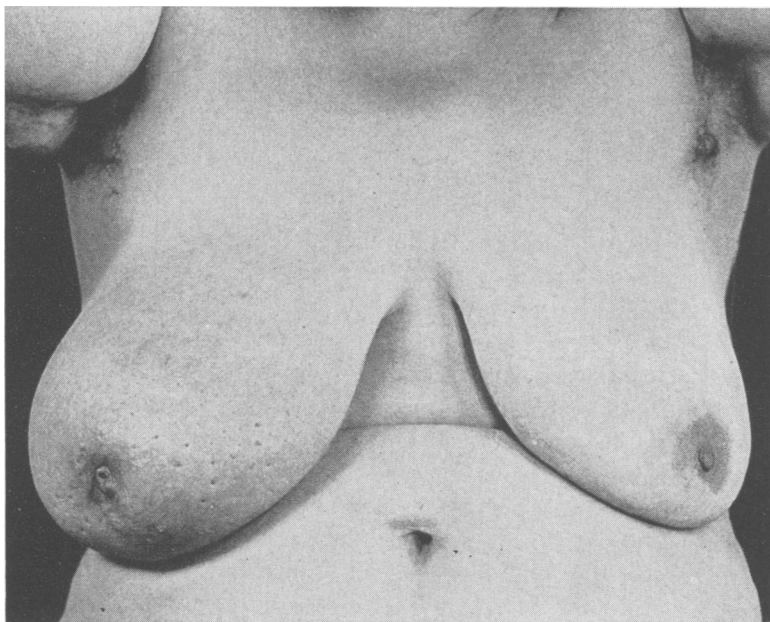


FIG. 4.—The inflammatory type of breast carcinoma.

that is in 4.9 per cent. Supraclavicular dissection was done in a total of 16 cases. In four of these, histologic examination showed the nodes were not involved. In the group of 12 remaining cases, in which the nodes did contain metastases, there were no five-year cures. Only four of these dissections were carried out at the time of the radical mastectomy. Three of the others were operated upon as a separate procedure shortly after radical mastectomy. In the remaining five cases the dissection was done at the time the supraclavicular nodes became palpable, from 10 to 48 months after radical mastectomy.

This experience has convinced us of the futility of supraclavicular dissection in patients in whom supraclavicular nodes are palpable. We have, therefore, classified these patients in our *categorically inoperable* group.

The use of supraclavicular dissection as a prophylactic procedure for

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patients in whom there is no clinical evidence of supraclavicular metastases but who have proved axillary involvement, is not so easily dismissed. The dissection, if properly done, is practically without mortality when carried out as a separate procedure subsequent to radical mastectomy. Since radiation, in our experience, will not cure supraclavicular metastases, surgeons who are willing to undertake a great amount of operating to salvage only three or four patients out of every hundred, may one day take up supraclavicular dissection again for use in carefully selected cases. It is a poor resource, but it is the best that we have.

INFLAMMATORY CARCINOMA OF THE BREAST

In any discussion of operability the so-called *inflammatory* type of breast carcinoma merits special consideration. In recent years this acute and fatal form of the disease has been well described by American and German writers. Taylor and Meltzer included a comprehensive bibliography in their 1938 paper.

The accompanying photograph (Fig. 4) shows a typical example of this disease. The patient, Hosp. No. 383920, a woman, age 58, came to the hospital complaining of a tumor of the breast of six weeks' duration. The right breast was almost twice the size of the left one, and the skin over it was reddened, edematous, and warmer than the skin over the other breast. Although the entire breast was indurated, there was, in addition, a hard tumor, measuring about 12 cm. in diameter, in the center of the organ. The nipple was retracted. In the right axilla there was a mass of hard nodes measuring 3 cm. in diameter, transversely. A radical mastectomy was performed. As might be expected with this type of disease there was prompt local recurrence in the field of operation on the chest wall, and the patient died with liver metastases, eight months after operation and nine and one-half months after the onset of her disease.

In the series of cases which we are reporting here there was a total of 28 patients with the inflammatory type of carcinoma. In 20 of them radical mastectomy was performed. Half of these were known to have developed local recurrence, and all succumbed to their disease within a relatively short time after operation. Some of the data regarding this group of cases are presented in Table XVIII.

This experience has led us to regard these patients with the inflammatory type of breast carcinoma as being incurable by operation. We classify them as *categorically inoperable*, and advise palliative treatment with radiation.

DISTANT METASTASES

A final factor in deciding as to the operability of breast carcinoma is the question of the presence of distant metastases. Every surgeon, of course, searches for them, but their demonstration is not always easy even with the best of our modern diagnostic aids.

TABLE XVIII

RESULTS OF RADICAL MASTECTOMY IN THE INFLAMMATORY TYPE OF TREATED CARCINOMA

A—Number of cases of <i>inflammatory</i> type in which radical mastectomy was carried out.....	20
B—Age of patients—varied from 38 to 61. Mean Age.....	47 years
C—Duration of symptoms on admission—varied from 1 week to 2 years. Mean duration.....	7.4 months
D—Symptoms:	
1—Pain.....	10
2—Tenderness.....	4
3—Diffuse enlargement of the breast.....	15
4—Widespread redness of skin over breast.....	20
5—Increased warmth of skin.....	5
6—Extensive edema of skin.....	19
7—Tumor palpable within breast.....	13
8—Two tumors in breast.....	1
9—Diffuse induration of breast, without a discernible tumor.....	8
10—Elevated body temperature.....	3
E—Local recurrence in 10, or 50 per cent.....	
F—Five-year clinical cures in none.....	
G—Mean length of survival following operation.....	15.5 month

It is our personal practice to carry out the following routine in searching for distant metastases in every new patient:

1. Inquire particularly about the recent development of headache, and pain in the back and legs.
2. Inquire regarding recent cough or pain in the chest.
3. Run the hand gently over the skin of the back and chest. In this way small skin metastases which can not be seen can often be felt.
4. Palpate the opposite axilla and the supraclavicular regions for distant lymph node metastases.
5. Palpate the abdomen, with special attention to the liver.
6. Roentgenograms of the chest and skeleton.

Each one of these methods of inquiry has, at one time or another, enabled us to detect distant metastases, and prevented useless radical mastectomy. Before the days of radiation therapy there was some excuse for carrying out radical mastectomy upon patients with distant metastases, but today, with the palliative resource of radiotherapy at hand, the surgeon is certainly not justified in operating.

We have come to feel that the entire skeleton, with the exception of the forearms and hands, lower legs and feet, should be studied roentgenologically. We have seen isolated metastases in the humerus, skull, shoulder girdle, and lower femur that would have been missed if these bones had not been included. A skeletal study of this kind requires six 14- x 7-inch, and three 10- x 12-inch films, but we believe that this expense is well worth while.

The great majority of these breast carcinoma metastases in bone are osteolytic in type. In films of the lower spine and pelvis, gas bubbles in the bowel often produce areas of lesser density which must be distinguished from osteolytic metastases. The experienced roentgenologist usually is able to do this at a glance, but stereoscopic films may be required in some cases.

The differential diagnosis of osteolytic lesions in bone, occurring in a female in middle and later life, who has a breast tumor is not difficult.

On the basis of relative frequency they will be found to be due to metastases from the breast tumor in the overwhelming majority of cases. Myeloma and hyperparathyroidism, which also cause destructive lesions in bone, are rare diseases. Accompanying blood chemistry changes will serve to distinguish them when the roentgenologic appearance is equivocal. In the skull, the changes due to osteoporosis circumscripta and to fully developed Paget's disease (see Kasabach and Gutman¹⁴) may cause confusion, but the finding of sclerotic, osteoblastic Paget lesions elsewhere in the skeleton will usually settle the problem. In fully developed Paget's disease the elevated blood phosphatase is, of course, diagnostic. In one of the patients in the present series the skull changes of Paget's disease were for a time mistaken for metastases.

These resources will enable the experienced roentgenologist to make a definite diagnosis of metastases in the great majority of women with breast carcinoma accompanied by bone lesions. In cases in which vague bone lesions defy exact diagnosis even after careful stereoscopic study, and in which there is no clinical evidence to tip the balance of opinion, it has been our custom to assume that they do not represent metastases and to proceed with operation. This practice has not, to our knowledge, led us into the error of undertaking radical mastectomy upon inoperable cases.

But even when roentgenologic studies are negative, the presumptive diagnosis of bone metastasis can be made from the history alone in certain cases. This is particularly true of metastases to the thoracic and lumbar spine. The pain that most of these unfortunate patients develop is rather characteristic. They often describe its earliest manifestation as "stiffness" of the back. After a few weeks this becomes definite pain, which develops after exercise such as walking or standing up for long periods of time. The pain becomes steadily worse, limiting the patient's activity greatly. When she sits quietly, or lies in bed, she is perfectly comfortable, but getting up from a chair or out of bed becomes torture. The pain is usually centered in the back, but may radiate down either leg. It is markedly accentuated by jolting, as when the patient misses a step and comes down hard on one foot, or when the vehicle in which she is riding strikes a sharp bump. We have repeatedly made a presumptive diagnosis of metastasis to the spine in patients with this kind of a story whose roentgenograms were negative, and have withheld radical mastectomy. Radiotherapy is begun at once, and if the pain is relieved after an appropriate interval the response provides confirmation of the diagnosis. Further roentgenologic studies at monthly intervals will eventually provide proof of the presence of metastases.

The interval between the onset of pain and the roentgenologic demonstration of bone metastases from breast carcinoma is sometimes remarkably long. Lenz and Fried¹⁵ reported a series of cases of this kind; in one, 12 full months elapsed before the spinal metastases were identified roentgenographically. The explanation for this long delay is found in the studies made by Chasin.¹⁶ He found that in vertebrae, defects of from 1 to 1.5 cm.

diameter made by removing the spongiosa, could not be demonstrated by the usual anteroposterior roentgenogram. Even when practically the entire spongiosa was removed, leaving only the cortex and the superior and inferior plates of the vertebra intact, he was unable to demonstrate the defect by films taken anteroposteriorly. These findings were corroborated by Böhmig and Prévot¹⁷ who were unable to demonstrate artificial defects the size of a cherry in the vertebrae by means of roentgenograms. We must, therefore, assume that when spinal metastases of breast carcinoma finally become apparent roentgenographically, the disease has already destroyed a great part of the structure of the vertebrae.

In the series of cases of breast carcinoma which we are here reporting, distant metastases were demonstrated on admission to the hospital in a total of 85, that is, in 9.7 per cent. In seven of these 85 patients radical mastectomy was, nevertheless, carried out. The situation of the distant metastases in these seven patients is detailed in Table XIX.

TABLE XIX

SITUATION OF DISTANT METASTASES DEMONSTRATED PREOPERATIVELY IN SEVEN PATIENTS TREATED BY RADICAL MASTECTOMY

A—In lymph node of contralateral axilla, as proved by biopsy	1
B—In ovary, as indicated by the presence of a large lower abdominal tumor	1
C—In the liver, as indicated by liver enlargement	1
D—In the spine, as indicated roentgenologically	4

The reason for operating is not apparent from the records of some of these cases. In others, the operator chose to ignore the evidence of the presence of metastases on the basis of the philosophy of "giving the patient her one chance of cure, remote though it might be." The fallacy of this kind of thinking, of course, is that the patient in truth has no chance whatever of cure when the evidence of metastasis is definite. None of the seven patients listed above was cured.

It is our own practice to classify patients in which there is presumptive evidence of the presence of distant metastases as *categorically inoperable*. We treat them exclusively with radiation.

A RULE FOR JUDGING OPERABILITY

When our data regarding the results of radical mastectomy in the different groups of cases with the various clinical features which we have detailed above are combined into Master Tables, a rule for operability can be derived from them. The first Master Table includes only the groups of cases in which there were virtually no five-year clinical cures—the groups which we have classified as *categorically inoperable*. These are combined in Table XX.

The groups of cases in Table XX are not mutually exclusive. They total 74 cases, with a local recurrence rate of 48.6 per cent, and no permanent cures. Faced with these facts it is impossible to escape the conclusion

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TABLE XX

RESULTS OF RADICAL MASTECTOMY IN CATEGORICALLY INOPERABLE GROUPS OF CASES

Clinical Group	No. of Cases	5-Year Local No.	Recurrence Per Cent	5-Year Clinical No.	Cures Per Cent
Carcinoma developing during pregnancy or lactation.....	20	6	30.0%	1	(Recurrence after 6 yrs.)
Extensive edema of skin over breast.....	41	27	65.9%	None	
Satellite nodules in skin over breast.....	7	4	57.1%	None	
Intercostal or parasternal nodules.....	1	0		None	
Edema of the arm.....	3	2	66.7%	None	
Proved supraclavicular metastases.....	12	7	58.3%	None	
Inflammatory type of carcinoma.....	20	10	50.0%	None	
Distant metastases.....	7	1	14.3%	None	
Total.....	74	36	48.6%	1	(Recurrence after 6 yrs.)

that cases of this kind should not be operated upon. They are truly *categorically inoperable*.

There remain several clinical factors indicative of the local extent of the disease regarding which our data are not as conclusive, particularly when these factors are considered individually. These data are combined in Table XXI. The groups of cases are small, but it should be kept in mind that they include only the cases in which the particular clinical sign in question was the only grave sign present; moreover, the *categorically inoperable* cases have been excluded.

TABLE XXI

RESULTS OF RADICAL MASTECTOMY IN GROUPS OF CASES EACH FEATURED BY A SINGLE CLINICAL SIGN INDICATIVE OF THE LOCAL EXTENT OF THE DISEASE

(*Categorically Inoperable Cases Excluded*)

Clinical Signs	No. of Cases	5-Year Local No.	Recurrence Per Cent	5-Year Clinical No.	Cures Per Cent
1—A single tumor 10 cm., or more, in diameter....	12	2	16.7%	3	25.0%
2—Multiple tumors in one breast.....	9	3	33.3%	4	44.4%
3—Redness of the skin.....	23	6	26.1%	8	34.8%
4—Skin involvement.....	21	6	28.6%	6	28.6%
5—Ulceration.....	9	1	11.1%	2	22.2%
6—Edema of limited extent.....	32	13	40.6%	4	12.5%
7—Fixation of tumor to chest wall.....	18	7	38.9%	2	11.1%
8—Axillary lymph nodes, 2.5 cm., or more, in diameter, proved to contain metastases.....	10	2	20.0%	2	20.0%
9—Fixed axillary nodes, proved to contain metastases.....	7	1	14.3%	1	14.3%

From Table XXI it is apparent that the presence of any single one of these various clinical signs of the local extent of the breast carcinoma is not a sufficient contraindication to radical mastectomy. The cure rate is rather lower, however, in the last five groups of cases in Table XXI than in the first four groups. This fact led us to test out in our data the prognostic significance of the presence of combinations of the various individual clinical signs with one or more of these five relatively unfavorable clinical factors, namely, ulceration, edema of limited extent, fixation of the tumor to the chest wall, axillary lymph nodes 2.5 cm. or more in diameter, proved to contain metastases, and fixed axillary lymph nodes, proved to contain metastases. Table XXII shows the results of radical mastectomy in cases

with these combinations of clinical signs. Here again, the *categorically inoperable* cases have been excluded, as have been the cases listed in Table XXI in which the various clinical signs occurred singly.

TABLE XXII

RESULTS OF RADICAL MASTECTOMY IN GROUPS OF CASES EACH FEATURED BY A COMBINATION OF SIGNS INDICATIVE OF THE LOCAL EXTENT OF THE DISEASE

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence No.	5-Year Local Recurrence Per Cent	5-Year Clinical Cures No.	5-Year Clinical Cures Per Cent
1—10 cm. tumor, <i>with</i> 5, 6, 7, 8, or 9	7	2	28.6%	1	14.3%
2—Multiple tumors, <i>with</i> 5, 6, 7, 8, or 9	3	1	33.3%	0	
3—Redness of skin, <i>with</i> 5, 6, 7, 8, or 9	30	13	43.3%	6	26.4%
4—Skin involvement, <i>with</i> 5, 6, 7, 8, or 9	44	11	25.0%	8	18.2%
5—Ulceration, <i>with</i> 6, 7, 8, or 9	14	4	28.6%	1	7.1%
6—Edema of limited extent, <i>with</i> 5, 7, 8, or 9	17	12	70.6%	0	
7—Fixation of tumor, <i>with</i> 5, 6, 8, or 9	24	9	37.5%	2	8.3%
8—2.5 cm. axillary lymph nodes, proved metastases, <i>with</i> 5, 6, 7, or 9	13	8	61.5%	1	7.7%
9—Fixed axillary lymph nodes, proved metastases, <i>with</i> 5, 6, 7, or 8	14	7	50.0%	0	

These data regarding the significance of combinations of clinical signs are of little or no value in Groups 1 and 2, because the numbers of cases are too small. In Groups 3 and 4 the cure rate is certainly high enough to justify radical mastectomy. In the last five groups of cases in Table XXII, however, the cure rate is so low that we doubt that operation was worth while. These groups of cases are not mutually exclusive, but the total number of cases falling into Groups 5, 6, 7, 8 and 9 is 35. The disease recurred locally before the end of five years in 16, or 45.7 per cent of these, and only two patients, or 5.7 per cent, were well five years after operation. Both of them later developed local recurrence and died.

From these correlations we have drawn up a rule for judging operability in breast carcinoma as follows: *Women of all age-groups, who are in good enough general condition to run the risk of major surgery, should be treated by radical mastectomy, except as follows:*

1. When the carcinoma is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When satellite nodules are present in the skin over the breast.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular metastases are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two, or more, of the following signs of locally advanced carcinoma are present:
 - (a) Ulceration of the skin.
 - (b) Edema of the skin of limited extent (less than one-third of the skin over the breast involved).

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- (c) Fixation of the tumor to the chest wall.
- (d) Axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter, and proved to contain metastases by biopsy.
- (e) Fixation of axillary lymph nodes to the skin or the deep structures of the axilla, and proved to contain metastases by biopsy.

If these criteria had actually been followed in judging operability in the series of 640 radical mastectomies which we have reported, a total of 109 of the patients would not have been operated upon. Yet the number of patients permanently cured would not have been decreased by a single one. These facts are shown in Table XXIII:

TABLE XXIII
HAAGENSEN-STOUT CRITERIA OF OPERABILITY
APPLIED TO PRESBYTERIAN HOSPITAL SERIES OF RADICAL MASTECTOMIES
(1915-1934)

Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures		Permanent Cures
		No.	Per Cent	No.	Per Cent	
Cases in which radical mastectomy was actually performed (1915-1934).....	640	161	25.2%	231	36.1%	Many still well
Cases which we now would classify as <i>inoperable</i>	109	53	47.7%	3	2.8%	None
Cases which we now would classify as <i>operable</i>	531	109	20.5%	228	42.9%	Many still well

In the group of 109 cases which we would now, according to our rule for operability, classify as inoperable, there were three that remained well at the end of five years after operation. All three, shortly thereafter, developed local recurrence, with distant metastases, and died. Summaries of these cases follow:

Case 1.—Hosp. No. 64106: M. W., colored, age 38. The tumor developed while she was nursing her first baby. It was 2.5 cm. in diameter, and situated in the upper outer sector of the breast. No local signs of inoperability. Radical mastectomy; one axillary node found to be involved. She was well at the end of five years, but, at six years, local intercostal recurrence and pulmonary metastases developed. She died seven and one-half years after operation.

Case 2.—Hosp. No. 281668: L. P., age 43. Large, 14 x 12 x 8 cm., tumor filling the breast and fixed to the chest wall. Hard axillary nodes, more than 2.5 cm. in transverse diameter. Radical mastectomy; all nodes found to be involved. Well at the end of five years, but, ten months later, local recurrence appeared on the chest and in the axilla. Cervical metastases subsequently appeared, and she died eight years after operation.

Case 3.—Hosp. No. 302431: M. B., age 59. The tumor measured 5 x 4 cm. and was situated in the upper inner sector of the breast. It had ulcerated through the skin, and was solidly fixed to the chest wall. Radical mastectomy; two axillary nodes involved. Well at the end of five years, but local recurrence on the chest wall and pulmonary metastases at the end of seven years. Died seven and one-half years after operation.

While radical mastectomy in this group of cases, which we today classify as inoperable may, in rare instances, relieve the patient of evidence of her disease for as long as five or six years, there is another aspect of the

therapeutic problem which must not be lost sight of. It is the fact that the carrying out of a radical mastectomy in cases in which the carcinoma can not be wholly removed locally actually *shortens* the patient's life in the majority of instances. From our knowledge of the problem of the surgical attack upon cancer in general we, of course, know that any attempt at radical dissection which cuts through cancer tissue is futile. The cancer cells are disseminated throughout the wound and there is the possibility of their entering the blood stream as cancer emboli. Ordinarily, operations of this kind are followed by prompt local recurrence and by the development of distant metastases. We have repeatedly seen widespread distant metastases appear within a few months after radical mastectomy performed upon patients in whom the disease was locally entirely inoperable, quite as if the operator had produced a shower of cancer emboli.

The data as to length of survival in our series of cases (Table XXIV) substantiate this objection to the performance of radical mastectomy in inoperable cases. We have used as a basis for our comparison the data collected by Lazarus-Barlow and Leeming,¹⁸ and by Daland,¹⁹ as to the mean survival of patients with untreated mammary carcinoma.

TABLE XXIV

MEAN TOTAL DURATION OF BREAST CARCINOMA—ONSET TO DEATH—IN VARIOUS GROUPS OF CASES

A—Daland's series of 100 untreated cases	40.5 months
B—Lazarus-Barlow's series of 243 untreated cases	38.4 months
C—118 Presbyterian Hospital cases (1915-1934 series) regarded as inoperable and denied surgery and radiation	42.3 months
D—31 Presbyterian Hospital cases (1915-1934 series) regarded as inoperable and treated by simple mastectomy	38.0 months
E—104 Presbyterian Hospital cases (1915-1934 series) regarded as operable and treated by radical mastectomy, but now classified as inoperable according to Haagensen-Stout criteria	32.3 month

These data suggest that the performance of radical mastectomy in cases in which the disease is locally so far advanced that cure can not be obtained shortens the patient's expectation of life by about ten months. Simple mastectomy may also shorten life somewhat. In these days, when radiation is available almost everywhere, we feel that, in general, it is the preferable method of palliation in these incurable cases. When the local disease is not checked by radiation and threatens to become an objectionable fungating tumor, and primary closure of the wound through grossly uninvolved tissue is technically possible, simple mastectomy is sometimes useful. But, in general, the less surgery that is undertaken upon the patients with incurable disease the longer they will survive.

As we emphasized at the beginning of this paper, the decision as to incurability, or rather inoperability, of breast carcinoma is difficult. We have suggested a rule for deciding the question, but we do not regard it as a definitive solution. We hope that other surgeons will test the validity of our criteria of operability upon their own series of cases, and by the use of statistical methods such as we have employed add to the knowledge of the problem.

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